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# Quantitative assessment of white matter injury in preterm neonates: Association with outcomes.

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## Association with outcomes

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## ABSTRACT

**Objective:** To quantitatively assess white matter injury (WMI) volume and location in very preterm neonates, and to examine the association of lesion volume and location with 18-month neurodevelopmental outcomes.

**Methods:** Volume and location of WMI was quantified on MRI in 216 neonates (median gestational age 27.9 weeks) who had motor, cognitive, and language assessments at 18 months corrected age (CA). Neonates were scanned at 32.1 postmenstrual weeks (median) and 68 (31.5%) had WMI; of 66 survivors, 58 (87.9%) had MRI and 18-month outcomes. WMI was manually segmented and transformed into a common image space, accounting for intersubject anatomical variability. Probability maps describing the likelihood of a lesion predicting adverse 18-month outcomes were developed.

**Results:** WMI occurs in a characteristic topology, with most lesions occurring in the periventricular central region, followed by posterior and frontal regions. Irrespective of lesion location, greater WMI volumes predicted poor motor outcomes ($p = 0.001$). Lobar regional analysis revealed that greater WMI volumes in frontal, parietal, and temporal lobes have adverse motor outcomes (all, $p < 0.05$), but only frontal WMI volumes predicted adverse cognitive outcomes ($p = 0.002$). To account for lesion location and volume, voxel-wise odds ratio (OR) maps demonstrate that frontal lobe lesions predict adverse cognitive and language development, with maximum odds ratios (ORs) of 78.9 and 17.5, respectively, while adverse motor outcomes are predicted by widespread injury, with maximum OR of 63.8.

**Conclusions:** The predictive value of frontal lobe WMI volume highlights the importance of lesion location when considering the neurodevelopmental significance of WMI. Frontal lobe lesions are of particular concern. ***Neurology*® 2017;88:614–622**

## GLOSSARY

**CA** = corrected age; **GA** = gestational age; **IQR** = interquartile range; **IVH** = intraventricular hemorrhage; **IZ** = intermediate zone; **OR** = odds ratio; **PMA** = postmenstrual age; **PVL** = periventricular leukomalacia; **SVZ** = subventricular zone; **TEA** = term-equivalent age; **WMI** = white matter injury.

Very preterm neonates are at high risk of motor, cognitive, and language deficits across their lifespan.[1] Sensitive early neonatal markers of risk are needed to identify those infants who would benefit most from developmental interventions as well as to provide families reassurance when outcomes are expected to be favorable.

With advances in neonatal intensive care, white matter injury (WMI), the characteristic pattern of brain injury in preterm neonates, has shifted from periventricular leukomalacia (PVL) to small punctate lesions. Punctate WMI is most readily diagnosed on T1-weighted images acquired early in life as areas of hyperintensity.[2–4] Neuroimaging studies of preterm infants demonstrate that multifocal WMI is accompanied by altered white matter microstructure, disrupted white matter maturation, and reduced functional connectivity in motor, cognitive, and attention networks in the brain.[5–8] However, current clinical scores of WMI account for the

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Supplemental data at Neurology.org

From Neurosciences and Mental Health (T.G., E.G.D., V.C., S.P.M.), The Hospital for Sick Children Research Institute; Departments of Paediatrics (T.G., E.G.D., E.A., V.C., S.P.M.) and Diagnostic Imaging (H.M.B.), The Hospital for Sick Children and the University of Toronto; Cerebral Imaging Centre (M.M.C.), Douglas Mental Health Research Institute, Verdun; Department of Psychiatry (M.M.C.) and Biological and Biomedical Engineering (M.M.C.), McGill University, Montreal; and Department of Pediatrics (K.J.P., A.S., R.E.G.), University of British Columbia, and BC Children's Hospital Research Institute, Vancouver, Canada.

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number of lesions and their relative size by visual inspection, and are imperfect predictors of neurodevelopmental disability.[3,9–15] Thus, further research is required to delineate the specific role of WMI on neurodevelopmental outcomes, particularly when accounting for lesion location and volume quantitatively.[16–20]

We hypothesize that the total lesion volume and the spatial location of punctate WMI affect neurodevelopmental outcomes of children born preterm. Thus we sought to quantitatively assess the association between the volume and location of WMI identified on early MRI with motor, cognitive, and language function at 18 months corrected age (CA). To assess this relationship, we calculated the volume of WMI, and generated probabilistic WMI maps and odds ratio (OR) maps for outcomes in a prospective cohort of very preterm neonates. Probabilistic mapping of WMI in a neonatal brain template using nonlinear registration[21,22] enables the assessment of WMI on a voxel-wise basis across participants to determine the characteristic topology of WMI. OR maps[23] are complementary to these maps and describe the risk of adverse outcomes associated with a lesion in each voxel in the template.

## METHODS

**Study population and clinical evaluation.** A total of 216 very preterm neonates (113 boys, 52%) who were admitted to the neonatal intensive care unit at British Columbia's Women's Hospital, Canada, and delivered at 24–32 weeks of gestation were enrolled in this study over a 7-year period (2006–2012).[24] Newborns with antenatal infections, congenital malformations/syndromes, or a parenchymal hemorrhagic infarction >2 cm were excluded. The clinical characteristics of the cohort are described in table e-1 at Neurology.org.

**Standard protocol approvals, registration, and patient consents.** A written informed consent from the legal guardian of each participating neonate was obtained. This study was reviewed and approved by the Clinical Research Ethics Board at the University of British Columbia and BC Children's and Women's Hospitals.

**Neurodevelopmental outcomes.** A total of 184 infants (85.2%) had follow-up at 18 months CA (median age 18.6 months; interquartile range [IQR] 18.3–19.2). Examiners assessed the infants' neurodevelopmental abilities using the Bayley Scales of Infant and Toddler Development, third edition (Bayley III). The Bayley-III includes standardized composite scores for motor, cognitive, and language skills with means of 100 and SD of 15. Scores more than 1 SD below the mean (<85) were considered to reflect adverse outcome, otherwise (≥85) typical neurodevelopmental outcome. Fifty-nine of 66 surviving infants with WMI returned for neurodevelopment assessment. One of these infants had a shunt inserted, causing MRI distortion that precluded accurate quantification of WMI. Thus, 58 neonates with WMI and 18-month outcomes were included in the analysis (table e-2). No clinical differences were evident between infants who did or did not return for follow-up ($p > 0.05$).

**MRI and brain injury scoring.** Brain MRIs were acquired without sedation on a 1.5T Siemens Avanto scanner (Erlangen, Germany) early in life when the neonates were clinically stable (median age 32.1 wk; IQR 30.4–34) or at term-equivalent age (TEA) (median age 40.1 wk; IQR 38.7–42.0), as previously reported.[25]

Blinded to the medical history of each neonate, an experienced neuroradiologist (K.J.P.) assessed brain injury on the first scan: WMI, intraventricular hemorrhage (IVH), ventriculomegaly, and cerebellar hemorrhage. Severity of WMI was scored based on a 3-point scale (minimal = 1: ≤3 lesions of <2 mm; moderate = 2: >3 lesions or lesions >2 mm and <5% hemispheric involvement; severe = 3: >5% of the hemisphere).[10,25]

**Manual segmentation of WMI.** Without knowledge of neurodevelopmental outcomes, 2 trained raters delineated the WMI on the T1-weighted early in life images as areas of abnormal T1 shortening ± cystic degeneration. As described in Results, we focused on punctate WMI and labeled macrocystic lesions separately. WMI segmentation was performed with simultaneous coronal, sagittal, and axial views of the brain (figure e-1) using Display software (bic.mni.mcgill.ca/ServicesSoftwareVisualization). Tricubic interpolation was used for visualization as it permitted accurate and consistent segregation of the WMI from the surrounding structures.[26] The high signal intensity periventricular band in frontal white matter was not considered pathologic. Images were inspected to ensure that voxels with ambiguous signal intensity were not erroneously considered within the WMI segmentation. Experienced neonatal neurologists (V.C. and S.P.M.) reviewed the segmented WMI for quality control. Intrarater and interrater reliability was high (intrarater reliability: 0.85 and 0.84; interrater reliability: 0.81) using Dice Kappa (supplemental material). Total WMI volume was calculated based on the manual segmentation (figure e-1).

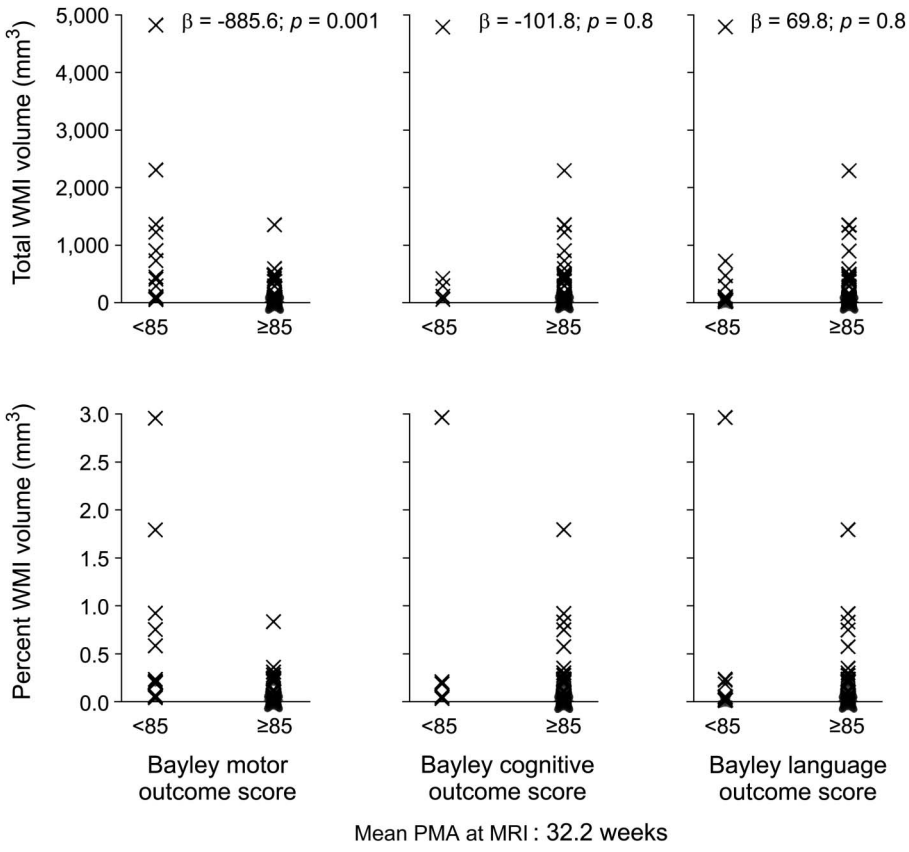
**Development of early preterm brain template and WMI maps.** ***Early preterm brain template.*** To compare the occurrence of WMI across participants within the cohort of very preterm neonates, we created an early preterm brain template using MICe build model (wiki.mouseimaging.ca/display/MICePub/MICe-build-model) with 137 T1-weighted early in life images (mean postmenstrual age [PMA] 31.2 weeks; range 27–33.9 weeks).

***Probabilistic WMI maps.*** The manually labeled WMI on each infant brain image was mapped to the common space of the early preterm template using a nonlinear transformation, which accommodates the anatomical variability between the patient and the template images.[21,22] The probabilistic WMI map was then generated based on the cumulative number of WMI lesions that occurred in homologous brain regions across participants in the standard template. The map permits the identification of WMI vulnerable regions, and whether the lesions occur in a characteristic spatial distribution.

We employed similar techniques to develop 3 WMI maps based on the motor, cognitive, and language outcomes assessed at 18 months CA. The WMI data that are unique to the neonates from typical and adverse outcome groups and those common to them are labeled in 3 distinguishable colors. As we hypothesized that neurodevelopmental outcomes are affected by WMI volumes and spatial location, these outcome-based WMI maps enable us to visually assess the differences in terms of WMI location between typical and adverse outcome groups intuitively.

To quantify the relationships between WMI location and outcome evident from the probabilistic maps, we calculated brain volumes in each of the 4 brain lobes (frontal, parietal, temporal,

**Figure 1** Noncystic white matter injury (WMI) volume in adverse and typical developmental outcome groups




The total WMI volumes and the percentage of WMI volume within the brain in the adverse and typical developmental outcome groups. The data on the left represent the WMI volumes of neonates who had adverse outcomes (Bayley III <85); those on the right are from neonates who had typical outcomes at 18 months corrected age. Some neonates with similar WMI volumes had different outcomes, indicating the WMI volume is not directly predictive of the outcome. The macrocystic lesion volumes were not included. The mean postmenstrual age (PMA) at MRI for the 58 neonates with WMI is 32.2 weeks and the median PMA is 32 weeks. Larger total WMI volumes are found in neonates with adverse motor outcomes (β = −885.6, $p = 0.001$), but not for cognitive (β = −101.8; $p = 0.8$) or language (β = 69.8; $p = 0.8$) outcomes.

occipital) delineated manually using Display software for regional WMI volumetric measurements (figure e-2).

**Statistical analyses examining the association of WMI and neurodevelopmental outcomes.** Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, v22; IBM, Armonk, NY). Clinical characteristics and demographic variables were compared using $\chi^2$ or Fisher exact tests for categorical data and Kruskal-Wallis tests for continuous data variables.

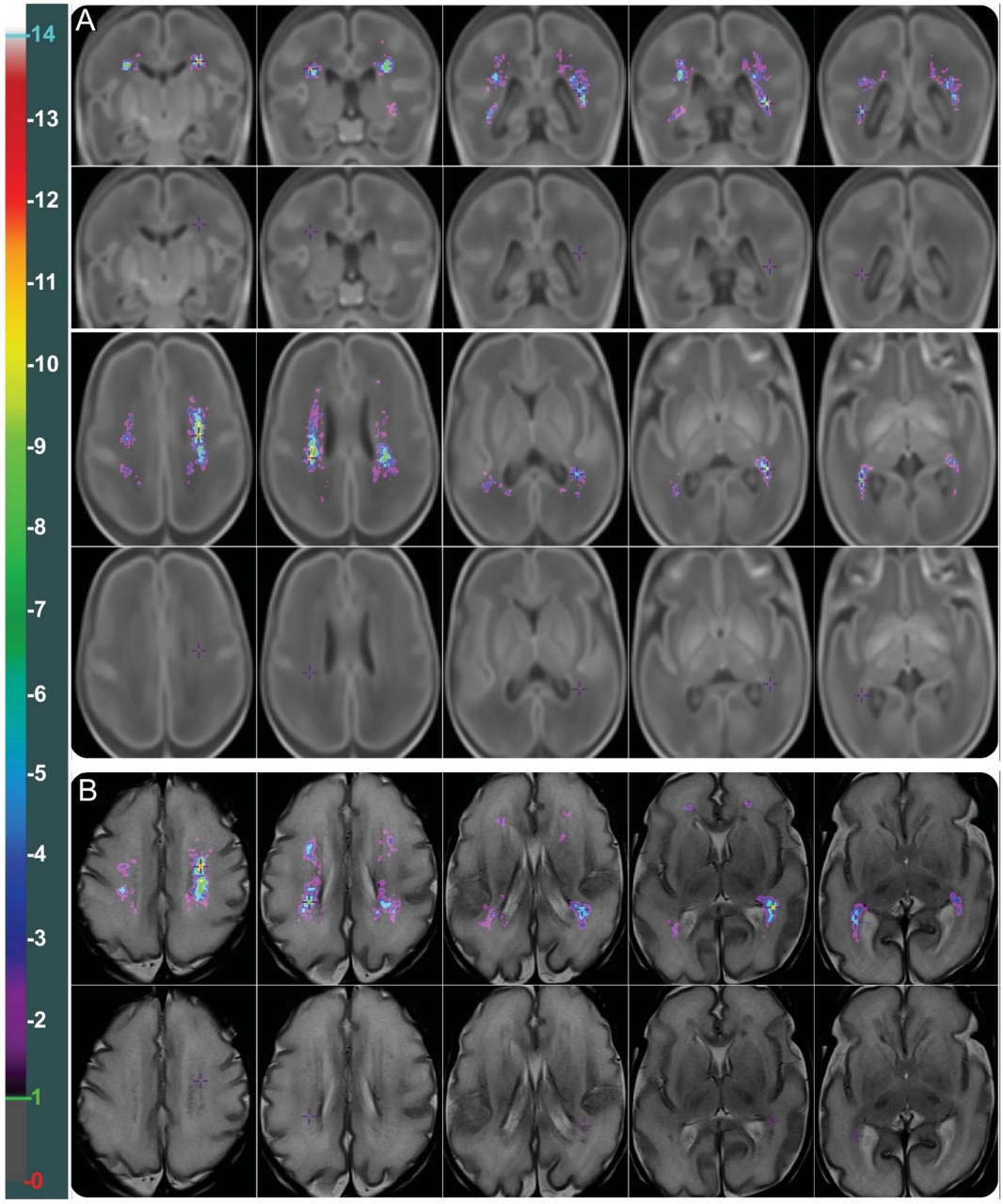
To assess whether greater WMI volume is associated with adverse neurodevelopmental outcomes, we used a multivariate linear regression to compare the total WMI volumes of neonates in the typical (Bayley III scores ≥85) and adverse outcome groups (scores <85) for motor, cognitive, and language outcomes, controlling for gestational age (GA), sex, age at scan, and brain volume. In subsequent analyses, we applied the same multivariate model to compare WMI lesion volume in each of the 4 brain regions (frontal, parietal, temporal, and occipital lobes) in neonates with typical and adverse outcomes. With our central hypothesis that WMI volume is associated with outcome, we consider $p$ values $< 0.05$ significant.

**OR maps of motor, cognitive, and language outcomes.** To determine whether lesion location is a better predictor of morbidity than is total lesion volume, we created voxelwise OR maps according to previously reported methods.[23] As an approach to synthesize lesion volume and location as a predictor of adverse neurodevelopmental outcomes, the OR maps quantify the levels of risk that WMI occurring at different anatomical regions pose for adverse outcomes (supplemental data).

**RESULTS Clinical evaluation of study participants.** Fifty-eight neonates with WMI and 124 without WMI identified on their early in life MRI had follow-up at 18-month CA (table e-1). Clinical factors as well as the level of maternal education did not differ in neonates with and without WMI ($p > 0.05$) (table e-1). Severe IVH and ventriculomegaly were uncommon in the study cohort; the incidence of IVH and ventriculomegaly did not differ based on the presence and absence of WMI (both $p > 0.05$, table e-1).

The median 18-month outcome scores are motor 97 (IQR 85–103), cognitive 108 (IQR 100–110), and language 103 (IQR 91–112). Only 2 of the 58 infants with WMI were diagnosed with moderate to severe cerebral palsy at 18 months

**Figure 2** Probabilistic white matter injury (WMI) map of 58 very preterm neonates on T1-and T2-weighted images

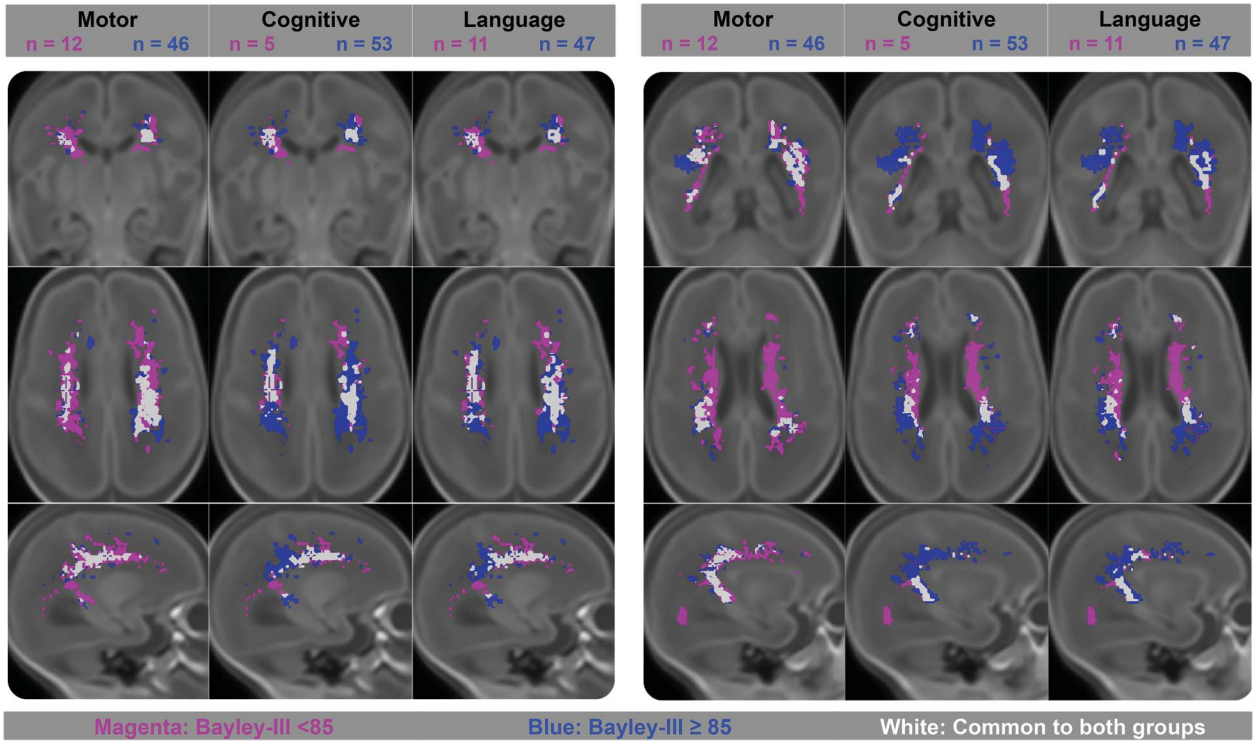



Probabilistic WMI map of 58 very preterm neonates overlaid on (A) the T1-weighted early preterm brain template and (B) a T2-weighted image. Noncystic WMI that occurred at a homologous region in 2 or more very preterm neonates are displayed. WMI seen only in a single neonate are omitted. (A) The cumulative (summed) WMI map of 58 neonates is overlaid on the neonatal brain template in coronal (top) and axial (bottom) planes. The axial planes along the superior to inferior direction are displayed from left to right in the figure. The color bar on the left indicates the color coding of the WMI summation. The maximum value on the map is 14. The cross on the coronal and axial planes of the T1-weighted brain template in each column with (top) and without (bottom) the WMI map is placed at the exactly identical location. (B) The probabilistic WMI map nonlinearly transformed and overlaid on the high-resolution T2-weighted image of a very preterm neonate (postmenstrual age [PMA] 29.7 weeks). First row: the probabilistic WMI map of 58 very preterm neonates nonlinearly transformed and overlaid on the T2-weighted image. Second row: the T2-weighted image. The lesions are seen in the subventricular zone and intermediate zone. The cross on the axial plane of the T2-weighted image in each column with (top) and without (bottom) the WMI map is placed at the same location.

(1 of these 2 infants had macrocystic lesions). Infants with severe WMI (grade 3) had lower motor scores ($p = 0.001$). The 18-month cognitive and language outcome scores did not differ among infants without WMI and with varying severities of WMI (table e-2).

Of the 58 neonates with WMI, 54 had scans at TEA. Consistent with previous reports,[10,27] WMI is most

**Figure 3** Motor, cognitive, and language outcome-based probabilistic white matter injury (WMI) maps




Probabilistic noncystic WMI map of 58 very preterm neonates based on the motor, cognitive, and language composite scores of Bayley III at 18 months of corrected age. Voxels in blue: WMI that are unique to the neonates who had typical outcomes (scores ≥85); voxels in magenta: WMI that are unique to the neonates who had adverse outcomes (scores <85); voxels in white: WMI common to neonates in both typical and adverse outcome groups. Left pane: the cross is at the territory of the left primary motor area in the neonatal template. Right pane: The cross is at territory of the right inferior parietal lobule in the brain template. The cross indicates the intersecting point for the coronal (top), axial (middle), and sagittal (bottom) planes on the left and the right panes.

apparent on the first scan: 24 neonates had less severe WMI at TEA and only one had more severe WMI.

**Quantitative measurements of WMI volumes and location.** Macrocystic lesions (volume ≥10 $mm^3$) were found in 2 neonates and were not considered in the primary analyses. Total volumes of punctate (i.e., noncystic) WMI varied dramatically from 4 $mm^3$ to 4,801 $mm^3$ (median 44 $mm^3$) (figure 1).

The WMI probabilistic map indicates that WMI occurs at homologous brain regions across participants and central regions are more prone to have WMI (figure 2A). The probabilistic WMI map overlaid on a high-resolution T2-weighted image revealed that WMI occurs most commonly in the intermediate zone (IZ) or outer subventricular zone (SVZ) (figure 2B).

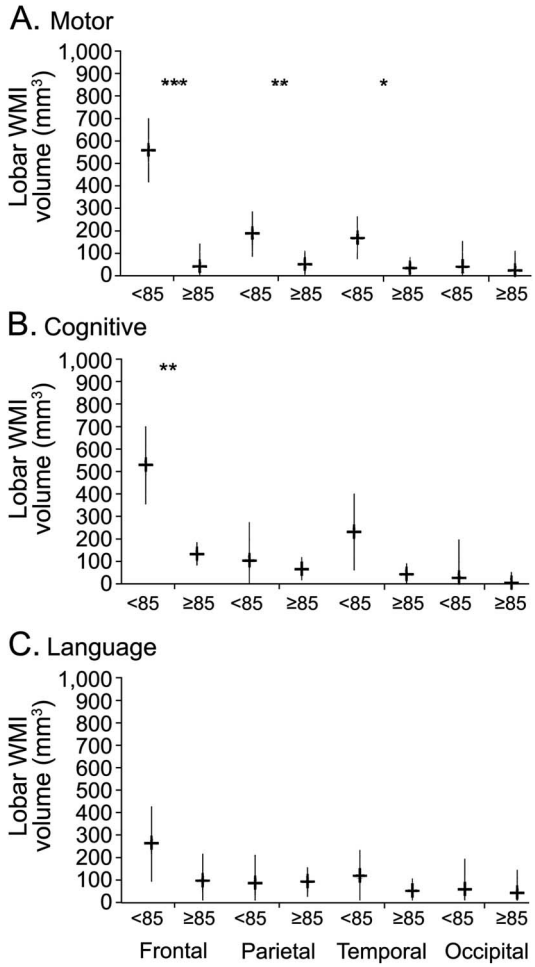
**Association of total WMI volumes with outcome.** Comparable absolute WMI volumes and WMI percentage of total brain volume are found in neonates in both outcome groups (figure 1). In multivariate models, neonates with adverse motor outcomes have larger total WMI volumes ($\beta = -885.6$, $p = 0.001$) relative to infants with typical motor outcomes accounting for GA, sex, age at scan, and total brain volume. In comparable models, total WMI volumes do not differ across cognitive ($\beta = -101.8$; $p = 0.8$) or language ($\beta = 69.8$; $p = 0.8$) outcome groups.

**Relationship between WMI location and outcome.** ***Qualitative assessment: Outcome-based WMI maps.*** When WMI is labeled relative to outcome, it is apparent that lesions common to both typical and adverse outcome groups are in the central and posterior regions (figure 3). Lesions only identified in neonates with adverse outcomes extend anteriorly to the frontal lobes; lesions solely seen in neonates with typical outcomes are distributed more posteriorly. Consistent with our hypothesis, the spatial location of WMI is predictive of outcome.

Of note, for the 2 neonates with anteriorly located macrocystic lesions, one had adverse motor, cognitive, and language outcomes, and one had only adverse motor outcomes.

***Quantitative assessment: WMI volumes by lobe.*** Accounting for GA, sex, age at scan, and total brain volume, infants with adverse motor outcomes had greater WMI volumes in frontal ($\beta = 541.2$, $p < 0.001$), parietal ($\beta = 166.9$, $p = 0.006$), and temporal ($\beta = 147.2$, $p = 0.03$) lobes. Adverse cognitive outcomes are associated with greater WMI in frontal lobes ($\beta = 413.2$; $p = 0.002$). Language outcomes are not associated with WMI volumes in any of the

**Figure 4** Lobar regional white matter injury (WMI) volume difference and neurodevelopmental outcomes




Regional differences between noncystic WMI volumes in the 4 brain lobes (frontal, parietal, temporal, and occipital) in relation to neurodevelopmental outcomes at 18 months ([A] motor; [B] cognitive; [C] language; Bayley III <85: adverse outcome; Bayley III ≥85: typical outcome). The symbols reflect estimated marginal means of the volumes. Error bars are the 95% confidence intervals. ***$p < 0.001$; **$p < 0.01$; *$p < 0.05$.

lobes ($p = 0.3$). These models are consistent with the probabilistic maps, indicating that frontal lobe WMI is most predictive of adverse motor and cognitive outcomes (figure 4).

***OR maps of motor, cognitive, and language outcomes.*** As an approach to account for lesion volume and location as predictors of outcome, OR maps (figure 5) demonstrate the odds of an adverse outcome if WMI occurs in a specific voxel. The brain region with the highest WMI occurrence rate (right posterior central region) is not associated with the highest risk of developing adverse outcomes. The OR maps illustrate that WMI at different locations poses different risks for adverse outcomes: the highest OR values for the motor, cognitive, and language maps are 63.8, 78.9, and 17.5, respectively.

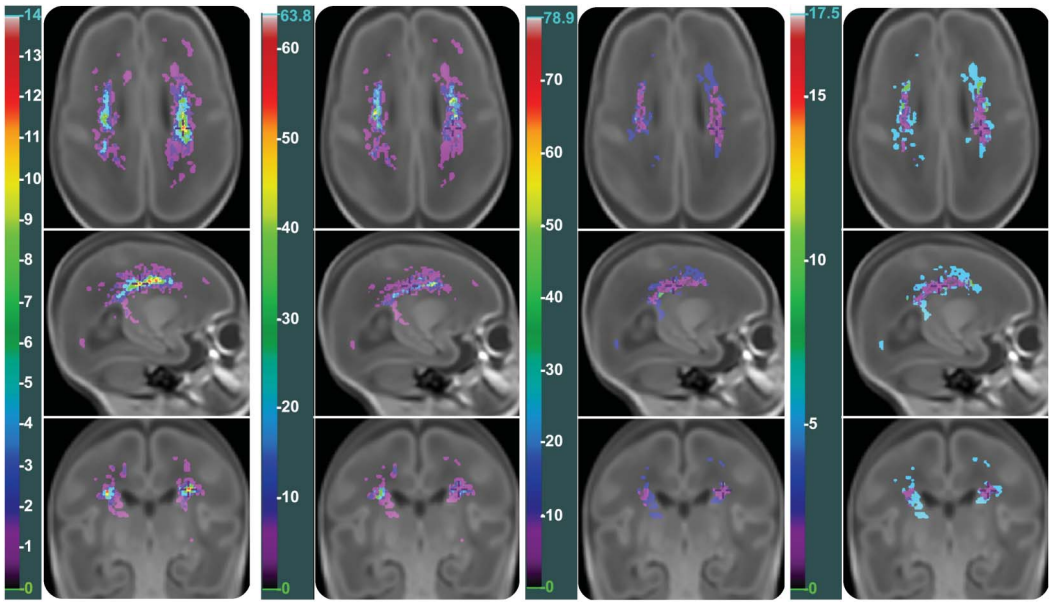
**DISCUSSION** In this prospective cohort of very preterm neonates, we demonstrate that WMI occurs in a characteristic pattern in circumscribed brain regions consistent with previous reports.[6,9,10] Yet total WMI volume alone does not accurately predict neurodevelopmental outcomes at 18 months CA. Outcome-based maps and OR maps indicate that lesion location in the frontal lobes is key to predicting adverse cognitive and motor outcomes. These findings should assist in counseling of families, including providing reassurance after the diagnosis of posteriorly located WMI, and will improve our ability to identify neonates for early developmental interventions or emerging strategies to promote brain repair.

When overlaid on a T2-weighted image to visualize the "white matter layers" in the third trimester of gestation, WMI appears to be primarily distributed in the SVZ and the IZ.[28] While distinguishing the IZ from the outer SVZ is difficult in the absence of specific histologic markers,[29,30] these findings are consistent with prior neuroradiologic assessment.[2,4] In the current work, WMI associated with the poorest outcomes was primarily located in the IZ of the frontal lobes. WMI may have affected the underlying connectivity of the striatum and frontal lobes, perhaps underlying the delays in cognitive and motor functions that are primarily subserved by these regions.[31]

The incidence of WMI peaks during a critical window of WM maturation and the establishment of critical neuronal connections and occurs in brain regions central to these processes. Neonatal WMI was previously linked to reduced cortical, thalamic, and basal ganglia volumes at TEA and later in childhood and adolescence.[11,32] Punctate WMI that appears hyperintense on T1-weighted MRI is accompanied by diffuse WMI characterized by preoligodendrocyte maturation arrest.[16,19,20,33] WMI is also related to dysmature white matter, microstructural abnormality, and abnormal functional connectivity.[5–8,25,34] Consequences of WMI may have been previously underestimated, as early multifocal lesions may affect microstructural and metabolic brain development over time in more widespread areas.[2] For example, increases in measures of neuronal metabolism in the neonatal brain were more strongly associated with neurodevelopmental outcomes in comparison to qualitative scoring of WMI severity.[25] In addition, the evolution of white matter fractional anisotropy from early in life to TEA has more prognostic significance than isolated values measured early in life.[5,25,35] We demonstrate that frontal WMI evident on early scans predicts adverse neurodevelopmental outcomes. Furthermore, the stronger association between lesion location rather than volumes with adverse neurodevelopmental outcomes supports the hypothesis that WMI results in disrupted frontal-striatal connectivity affecting later cognitive and motor abilities.

Although WMI is still visible on images at TEA, the burden of WMI in very preterm neonates is best

**Figure 5** Odds ratio (OR) maps of white matter injury (WMI) for adverse motor, cognitive, and language outcomes




OR maps of noncystic WMI for motor (second column), cognitive (third column), and language (fourth column) outcomes overlaid on the T1-weighted neonatal brain template. The first column shows the spatial cumulative WMI map including all noncystic WMI seen in any of the 58 very preterm neonates. Note the different scaling of the images in each column as indicated by each color bar. The purple cross is at exactly the same location in each of the 4 maps. The area with high WMI occurrence rate does not necessarily indicate high risk in developing adverse outcomes. The maximum OR values on the motor, cognitive, and language OR maps are 63.8, 78.9, and 17.5, respectively.

visualized on earlier T1-weighted MRI (median PMA of 32 weeks).[4,10,27,36] As the abnormal signal intensity of WMI resolves over time, measurement of WMI at TEA does not provide the most accurate lesion volume and location. Given this, we focused our assessment of the WMI lesions on the earlier scan when WMI volume and location is most readily measured.

Prior research revealed that moderate to severe WMI identified on MRI at TEA in very preterm infants was predictive of adverse neurodevelopmental outcomes at 2 years of age.[11] However, WMI was assessed at a time punctate lesions may be harder to detect, and quantitative lesion volumes and location were not established. Our quantitative analysis at a time most sensitive to WMI detection demonstrated that although the total WMI volume was significantly larger in infants with adverse motor outcomes, differences in lesion volumes were not evident between the cognitive and language outcome groups.

Illustrated on outcome-based probabilistic WMI maps, the lesions associated with adverse outcomes were more anteriorly distributed, while the lesions related to typical outcomes tended to be more posterior. By assessing the association of WMI volumes within different brain lobes with outcomes, we found that adverse motor and cognitive outcomes were associated with greater WMI volumes in frontal lobes. These findings indicate that lesion location contributes to the prediction of neurodevelopmental outcomes. Of note, macrocystic lesions were uncommon and contributed little to an increased risk of adverse outcome on the OR maps. Thus, at a population level, frontal macrocystic lesions are not the main contributors of neurodevelopment outcomes in contemporary practice. With evidence from a number of centers confirming a decline in macrocystic WMI (i.e., PVL),[37,38] our findings highlight the urgent need for strategies to prevent punctate WMI.

Detecting early or very small lesions, beyond the spatial resolution parameters afforded by MRI, is a limitation of our technique.[31] We also recognize that there are pathways to adverse outcomes in preterm neonates that are independent of WMI, such as severe IVH, as well as clinical factors for which specific imaging biomarkers are not yet available. Examining quantitative WMI maps in larger cohorts of neonates, particularly from multiple centers, will enable other aspects of clinical illness to be considered in prediction models. We also recognize that motor, cognitive, and language abilities assessed at 18 months of age are not extensive descriptors of children's long-term cognitive and physical abilities, nor their overall well-being. Future studies should consider developmental outcomes assessed in later childhood to specifically determine the longer-term impact of WMI.

In this article, we present evidence that punctate white matter lesions in the territory of frontal lobes

were associated with clinically significant adverse motor and cognitive outcomes at 18 months in very preterm neonates. Probabilistic WMI maps illustrate that WMI occurs in a characteristic spatial pattern across participants in the neonatal brain. Furthermore, both outcome-based and OR maps, as well as the quantitative assessment of WMI volumes within different lobes, demonstrate that lesion location adds important information to lesion volume when considering the neurodevelopmental trajectories of preterm neonates. The creation of the neonatal WMI probabilistic and OR maps will facilitate the analysis of other neurologic conditions associated with WMI for better understanding of how these insults affect brain function and relate to outcome.

## AUTHOR CONTRIBUTIONS

T.G., E.G.D., E.A., V.C., M.M.C., K.J.P., A.S., R.E.G., and S.P.M. contributed to the conception and design. T.G., E.G.D., E.A., V.C., H.B., M.M.C., K.J.P., A.S., R.E.G., and S.P.M. contributed to the data acquisition and analysis. T.G., E.G.D., V.C., and S.P.M. contributed to drafting the manuscript and figures. All authors contributed to editing the manuscript for content.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## DISCLOSURE

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